UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

DANA-FARBER CANCER INSTITUTE, INC., Plaintiff, v. ONO PHARMACEUTICAL CO., LTD., TASUKU HONJO, E.R. SQUIBB & SONS, L.L.C., and BRISTOL-MYERS SQUIBB CO., Defendants.	)	C.A. No. _____

COMPLAINT

Dana-Farber Cancer Institute, Inc. ("Dana-Farber"), for its complaint against Ono Pharmaceutical Co., Ltd. ("Ono"), Tasuku Honjo ("Honjo"), E.R. Squibb & Sons, L.L.C. ("Squibb"), and Bristol-Myers Squibb Co. ("BMS"), alleges as follows:

Introduction

1. This is an action to correct inventorship under 35 U.S.C. § 256 with respect to five United States patents: United States Patent No. 7,595,048 (the "'048 patent"); United States Patent No. 8,168,179 (the "'179 patent"); United States Patent No. 8,728,474 (the "'474 patent"); United States Patent No. 9,067,999 (the "'999 patent"); and United States Patent No. 9,073,994 (the "'994 patent") (collectively, the "Patents"). Copies of the Patents are attached hereto as Exhibits A through E, respectively. The Patents are co-assigned to Ono and Honjo. Honjo and three of his Kyoto University colleagues, Nagahiro Minato, Yoshiko Iwai, and Shiro Shibayama, are named as inventors on the Patents.

2. This case concerns a pioneering development in the treatment of cancer, in particular, a new means to treat cancer using a technique called "cancer immunotherapy."

Cancer immunotherapy is a way to unleash the body's own disease-fighting cells—the immune system's T lymphocytes, or "T cells"—to make a sustained attack on cancer cells. T cells are a critical component of the body's immune system, recognizing and protecting against viruses and other foreign invaders and also helping to destroy cancer cells.

3. Critical research that made cancer immunotherapy possible took place at Dana-Farber in the 1990s, led by Dana-Farber scientist Gordon J. Freeman, Ph.D. Freeman is a researcher in the Department of Medical Oncology at Dana-Farber and Professor of Medicine at Harvard Medical School. In the course of his research at Dana-Farber, Freeman discovered that a particular protein carried on the surface of many human cells helps the cells avoid being attacked by the immune system's T cells. This protein, called PD-L1, does so by interacting with a complementary protein on the surface of T cells called PD-1 ("PD" is an acronym for "programmed cell death"). When the PD-L1 on a normal cell binds to PD-1 on a T cell, the effect is to inhibit (or "downregulate") the proliferation of T cells, as well as the T cells' expression of certain immune proteins called cytokines. In this way, the PD-1/PD-L1 interaction prevents an individual's T cells from launching an immune response against his or her own normal cells, and in doing so provides a critical checkpoint against autoimmune disease. Because of this property, PD-1 is sometimes referred to as an "immune checkpoint protein."

4. Although the existence of PD-1 on T cells was discovered earlier in the 1990s, its biological function remained unclear to scientists until Freeman identified its specific binding partner ("ligand"), PD-L1. Only then was PD-1's function in T cell regulation, and the existence of the PD-1/PD-L1 pathway, unveiled. Freeman later identified the existence of a second ligand for PD-1, now known as PD-L2.

5. Freeman also discovered that certain cancer cells carry large numbers of PD-L1 protein on their surfaces. This allows the cancer cells to interact with PD-1 on T cells and use the same mechanism normal cells use to suppress an immune response against them. This allows the cancer cells to live on and multiply while escaping attack from the body's T cells.

6. Cancer immunotherapy in effect unmasks the cancer cells for what they are and allows the immune system to do its job. This technique uses therapeutic antibodies to block either PD-L1 on cancer cells or PD-1 on T cells so that their interaction is disrupted and the immune checkpoint is no longer available to the cancer cells.

7. The PD-1/PD-L1 pathway can be analogized to a biological lock and key. When PD-L1 is expressed on a normal cell and finds PD-1 on a T cell, it "unlocks" the immune checkpoint, preventing an overactive immune response such as occurs in autoimmune disease. To treat cancer, the goal is the opposite: to prevent PD-L1 on cancer cells from binding to PD-1 on T cells, thus encouraging a more powerful immune response against the cancer cells. This can be done using antibodies to block either PD-L1 or PD-1. Applying the lock and key analogy, one can either change the lock or alter the key; either way, the cancer cells are unable to open the door to the immune checkpoint. By this innovative new technique, the command that once prevented or weakened the immune system's attack on cancer is lifted, and the body's own natural defenses are allowed to fight the disease.

8. In 2014, Honjo and Freeman were both recipients of the Cancer Research Institute's William B. Coley Award for Distinguished Research in Tumor Immunology, its top scientific prize, for their "contributions to the discovery of the PD-1 pathway."

9. The Patents, issued between 2009 and 2015, claim that the idea of blocking the PD-1/PD-L1 pathway as a means to allow T cells to attack cancer cells was the sole invention of

Honjo and colleagues at Kyoto University in Japan. In fact, as described below, the Patents resulted from a collegial and highly successful research collaboration among three institutions. The collaboration included not only Honjo at Kyoto University, but also Freeman at Dana-Farber and Clive R. Wood, Ph.D. at Genetics Institute ("GI"), a Cambridge, Massachusetts biotechnology company. The three of them worked together to reveal the mysteries of the PD-1/PD-L1 interaction. Through correspondence and in-person meetings that took place at GI in Cambridge, they shared their knowledge, their ideas, their experimental data, and their drafts of scientific publications to arrive at the conception of the inventions claimed in the Patents. Honjo, Freeman, and Wood all contributed to conception of subject matter claimed in the Patents, and all three are joint inventors of the inventions claimed in the Patents.

10. Once their discoveries were shared with the scientific community, pharmaceutical companies began clinical testing of antibodies against PD-1 and PD-L1. In 2014, the United States Food and Drug Administration ("FDA") approved two antibodies against PD-1, OPDIVO® developed by BMS and Squibb, and KEYTRUDA®, developed by Merck, for treatment of advanced melanoma.

The Parties

11. Dana-Farber is a Massachusetts non-profit corporation with a place of business at 450 Brookline Avenue, Boston, Massachusetts 02215. Since its founding in 1947, Dana-Farber has been committed to providing adults and children suffering from cancer with the best treatments available today while also developing future therapies through cutting-edge research. As an affiliate of Harvard Medical School and a Comprehensive Cancer Center designated by the National Cancer Institute, Dana-Farber also provides training for new generations of physicians and scientists; designs programs that promote public health, particularly among high-risk and

underserved populations; and disseminates innovative patient therapies and scientific discoveries across the United States and throughout the world.

12. Dana-Farber is the assignee of Freeman's rights and interest as an inventor in the inventions claimed in the Patents.

13. On information and belief, Ono is a corporation organized under the laws of Japan, with a place of business at 8-2 Kyutaromachi 1-chome, Chuo-ku, Osaka 541-8654, Japan.

14. On information and belief, Honjo is an individual with a place of business at Kyoto University, Graduate School of Medicine, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan.

15. Ono and Honjo are co-assignees of each of the Patents. On information and belief, Ono and Honjo have exclusively licensed their rights under the Patents to BMS and Squibb.

16. On information and belief, BMS is a corporation organized under the laws of the State of Delaware, with a principal place of business at 345 Park Avenue, New York, New York 10154.

17. On information and belief, Squibb is a limited liability company organized under the laws of the State of Delaware, with a principal place of business at Route 206 & Province Line Road, Princeton, New Jersey 08543.

Jurisdiction

18. The Court has jurisdiction over this action under 28 U.S.C. §§ 1331, 1338 and 35 U.S.C. § 256.

19. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b), (c).

20. This Court has personal jurisdiction over Ono, Honjo, Squibb, and BMS to adjudicate this action for correction of inventorship under 35 U.S.C. § 256.

The Freeman/Wood/Honjo Collaboration

21. In the 1990s, Freeman was investigating the "B7" family of proteins. Two of the proteins in this family, called B7-1 and B7-2, were known to be ligands critical to the regulation of the immune response. Early in an immune response, B7-1 and B7-2 bind to a receptor on the surface of T cells referred to as CD28, which produces a "co-stimulatory" signal that contributes to the activation of T cells, causing their proliferation and enhancing an immune response. Later in an immune response, the activated T cells begin expressing a second receptor, called CTLA-4, that is also able to bind to B7-1 and B7-2. However, whereas the binding of CD28 by B7-1 and B7-2 enhances the immune response, the binding of the B7 ligands to CTLA-4 has the opposite effect, producing an inhibitory signal that keeps the immune response in check and reduces the damage the immune response causes to healthy tissue.

22. Through this work, Freeman came to believe that there would be additional B7-like and CD28-like receptor/ligand pairs, not yet discovered, that would play a similar role in T cell activation. One such ligand he discovered was a receptor on mouse T cells called ICOS. Freeman's work on ICOS was conducted through a research collaboration with scientists at GI in Cambridge, Massachusetts, including Wood. This work led to the identification of a B7-like molecule that was a ligand for ICOS.

23. Through further investigation of B7-like proteins, Freeman discovered a novel protein he called "B7-4," or "292." After experimentation in his lab at Dana-Farber, Freeman isolated the full-length complementary DNA ("cDNA") that encodes the 292 protein. Freeman transferred the cDNA for 292 to GI for further study, telling Wood about his discovery that the protein was expressed in antigen-presenting cells ("APC's") and inhibited T cell activation. (Later, in 2000, this protein was renamed "PD-L1," and for convenience, it is referred to herein as PD-L1.)

24. In the meantime, Wood had been conducting studies on the PD-1 protein. PD-1 had been known since the early 1990s, but its biological function and mechanism of action were not known. Wood was conducting investigations to identify molecules that would interact with PD-1 in order to better understand its function. To facilitate this, at Wood's request, Honjo provided Wood with the cDNA that encoded PD-1.

25. Wood's experiments indicated that Freeman's PD-L1 molecule bound to PD-1. In other words, PD-L1was the missing ligand for PD-1.

26. On August 23, 1999, Freeman and Wood filed a provisional patent application describing their discovery that PD-1 is a receptor for PD-L1, and that the interaction between PD-1 and PD-L1 results in modulation of the immune response.

27. Thereafter, Wood facilitated an introduction of Freeman to Honjo and arranged a meeting at GI's offices in Cambridge.

28. The meeting took place on October 25, 1999. At the meeting, Freeman, Wood, and Honjo freely shared their research and agreed to collaborate with respect to the PD-1/PD-L1 pathway. The work of Freeman and Wood demonstrating binding of PD-L1 to PD-1 had not yet been published. Honjo learned of this discovery for the first time from his interactions with Wood and Freeman.

29. At the meeting, Freeman discussed the unpublished experimental data reported in the Freeman/Wood provisional patent application. Freeman shared with Honjo, among other things, the cDNA sequence encoding PD-L1, a sequence comparison between PD-L1 and other members of the B7 family of co-stimulatory proteins, and data showing the expression of PD-L1 on various types of cells. Wood shared with Honjo PD-1 fusion protein-binding data, data from the interaction of anti-PD-1 antibodies with T cells, data from T cell proliferation assays, and

experiments conducted by GI and Dana-Farber showing the inhibition of T cell activation when PD-1 was engaged by a PD-L1 immunoglobulin fusion protein.

30. Freeman also shared with Honjo that the cDNA sequence partially encoding PD-L1 (an expressed sequence tag, "EST"), which Freeman had found in a genetic database and had used to isolate the full-length sequence of PD-L1, had come from human ovarian tumor cells, meaning PD-L1 was expressed by at least some cancer cells.

31. At the meeting, although Honjo's presentation concerned possible ways to engage the PD-1/PD-L1 pathway to treat autoimmune disease by downregulating the immune response, Freeman raised the possibility of blocking the pathway in order to enhance, or upregulate, the immune response to cancer.

32. Immediately following the meeting, Freeman and Honjo agreed that Freeman would send Honjo the cDNA for PD-L1 and cells engineered to produce PD-L1 protein. They agreed that Honjo, in turn, would permit Wood to send to Freeman the PD-1 antibodies made by Honjo (as Honjo had previously sent to Wood) and the PD-1-immunglobulin fusion protein made by Wood using Honjo's PD-1 cDNA. Confirming this, on November 2, 1999, Honjo executed a Dana-Farber Material Transfer Agreement for the transfer to Honjo of murine and human cDNA encoding PD-L1 and related know-how. The agreement identified the subject of Honjo's research using these materials as "collaborative research." Freeman sent the PD-L1 materials to Honjo later that month.

33. In the course of the collaboration, the three scientists continued their experiments, including experiments to block the PD-1/PD-L1 pathway; shared their data; and co-authored a scientific paper reporting their discoveries. Beginning in December 1999, they exchanged numerous drafts of the paper, and each contributed his comments and suggestions. The paper

eventually was published as Freeman et al., "Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation," J. Exp. Med., October 2, 2000.

34. The paper describes Freeman's search for B7-like molecules and Wood's testing of the binding of PD-L1 to PD-1. The paper demonstrates that the PD-1/PD-L1 interaction leads to the inhibition of lymphocyte proliferation. The paper contains five figures reporting experimental data. Freeman contributed Figure 1, and Wood contributed Figure 5. Freeman and Wood contributed Figures 2 and 3. Honjo and Wood contributed Figure 4.

35. At Freeman's suggestion, the paper reports that PD-L1 is expressed in some cancers, "rais[ing] the possibility that some tumors may use PD-L1 to inhibit an anti-tumor immune response."

36. In 2000, further experiments were conducted and additional data shared among the three scientists. On October 5, 2000, Honjo executed another Material Transfer Agreement with Dana-Farber, under which Dana-Farber provided Honjo with anti-human PD-L1 antibody to use in Honjo's experiments. Honjo, Freeman, and Wood met on October 8, 2000 at GI's offices in Cambridge to discuss their collaborative research and share their ideas.

37. In 2000, Freeman undertook to investigate the expression of PD-L1 on a variety of tissues and tumor cells. Freeman shared his data with Honjo and Wood as part of their collaboration. Freeman's research showed that PD-L1 is highly expressed in a number of tumor cell lines, including lung and breast cancer malignancies, many ovarian tumors, and some tumor lines of lymphohematopoietic origin. These findings led to the suggestion in a 2001 paper they co-authored that "blocking the PD-1 pathway may enhance anti-tumor immunity," and that the pathway "may be an attractive therapeutic target." Latchman et al., "PD-L2 is a second ligand

for PD-1 and inhibits T cell activation," Nature Immunology, March 2001. Drafts of this paper were exchanged among Freeman, Wood, and Honjo prior to publication, and each contributed comments and ideas to the final paper. Seven of the eight figures in the paper were contributed by Freeman based on experiments he supervised; Freeman and Wood contributed to the remaining figure.

The Patents

38. On July 3, 2002, Honjo and three colleagues at Kyoto University filed Japanese Patent Application 2002-194491. One year later, they converted their application into PCT Application No. PCT/JP03/08420. According to their disclosure, the applicants "found that the substances that could inhibit the inhibitory signals of PD-1, PD-L1, or PD-L2 hav[e] therapeutic potential for cancer or infection and completed the present invention."

39. On September 29, 2009, the United States Patent Office issued the '048 patent, entitled "Method for Treatment of Cancer by Inhibiting the Immunosuppressive Signal Inducted by PD-1." The '048 patent claims priority to the July 3, 2002 Japanese Patent Application and a second Japanese Patent Application filed on February 6, 2003. The '048 patent is co-assigned to Honjo and Ono. It names as inventors Honjo and the three Kyoto University colleagues, Nagahiro Minato, Yoshiko Iwai, and Shiro Shibayama. Neither Freeman nor Wood is named as an inventor.

40. Claim 1 of the '048 patent is representative: "A method for treatment of cancer, wherein a pharmaceutically effective amount of completely human anti-PD-1 antibody is parenterally administered to a subject with cancer in which PD-L1 or PD-L2 is over-expressed, postoperatively."

41. On May 1, 2012, the United States Patent Office issued the '179 patent, entitled "Treatment Method Using Anti-PD-L1 Antibody." The '179 patent also claims priority to the

July 3, 2002 Japanese Patent Application and a second Japanese Patent Application filed on February 6, 2003. The ’179 patent shares a common specification with the ’048 patent. The ’179 patent is co-assigned to Honjo and Ono. It names as inventors Honjo and the three Kyoto University colleagues, Nagahiro Minato, Yoshiko Iwai, and Shiro Shibayama. Neither Freeman nor Wood is named as an inventor.

42. Claim 1 of the ’179 patent is representative: “A method of treating a PD-L1-expressing tumor, comprising administering a pharmaceutically effective amount of an anti-PD-L1 antibody to a patient in need thereof, in combination with a pharmaceutically effective amount of one or more chemotherapy drugs, wherein said one or more chemotherapy drugs are selected from the group consisting of an alkylating agent, a nitrosourea agent, an antimetabolite, an antitumor antibiotic, an alkaloid derived from a plant, a topoisomerase inhibitor, a hormone therapy medicine, a hormone antagonist, an aromatase inhibitor, a P-glycoprotein inhibitor and a platinum complex derivative.”

43. On May 20, 2014, the United States Patent Office issued the ’474 patent, entitled “Immunopotentiative Composition.” The ’474 patent also claims priority to the July 3, 2002 Japanese Patent Application and a second Japanese Patent Application filed on February 6, 2003. The ’474 patent shares a common specification with the ’048 patent and the ’179 patent. The ’474 patent is co-assigned to Honjo and Ono. It names as inventors Honjo and the three Kyoto University colleagues, Nagahiro Minato, Yoshiko Iwai, and Shiro Shibayama. Neither Freeman nor Wood is named as an inventor.

44. Claim 1 of the ’474 patent is representative: “A method for treatment of a tumor in a patient, comprising administering to the patient a pharmaceutically effective amount of an anti-PD-1 monoclonal antibody.”

45. On June 30, 2015, the United States Patent Office issued the ’999 patent, entitled “Immunopotentiative Composition.” The ’999 patent also claims priority to the July 3, 2002 Japanese Patent Application and a second Japanese Patent Application filed on February 6, 2003. The ’999 patent shares a common specification with the ’048 patent, the ’179 patent, and the ’474 patent. The ’999 patent is co-assigned to Honjo and Ono. It names as inventors Honjo and the three Kyoto University colleagues, Nagahiro Minato, Yoshiko Iwai, and Shiro Shibayama. Neither Freeman nor Wood is named as an inventor.

46. Claims 1 and 19 of the ’999 patent are representative. Claim 1 recites: “A method of treating a lung cancer comprising administering a composition comprising a human or humanized anti-PD-1 monoclonal antibody to a human with the lung cancer, wherein the administration of the composition treats the lung cancer in the human.” Claim 19 recites: “The method of claim 1, wherein the lung cancer expresses PD-L1.”

47. On July 7, 2015, the United States Patent Office issued the ’994 patent, entitled “Immunopotentiative Composition.” The ’994 patent also claims priority to the July 3, 2002 Japanese Patent Application and a second Japanese Patent Application filed on February 6, 2003. The ’994 patent shares a common specification with the ’048 patent, the ’179 patent, the ’474 patent, and the ’999 patent. The ’994 patent is co-assigned to Honjo and Ono. It names as inventors Honjo and the three Kyoto University colleagues, Nagahiro Minato, Yoshiko Iwai, and Shiro Shibayama. Neither Freeman nor Wood is named as an inventor.

48. Claims 1 and 14 of the ’994 patent are representative. Claim 1 recites: “A method of treating a metastatic melanoma comprising intravenously administering an effective amount of a composition comprising a human or humanized anti-PD-1 monoclonal antibody and a solubilizer in solution to a human with the metastatic melanoma, wherein the administration of

the composition treats the metastatic melanoma in the human." Claim 14 recites: "The method of claim 1, wherein the metastatic melanoma expresses PD-L1."

49. The Patents report additional experiments by Honjo and colleagues using antibodies that block PD-1 or PD-L1 to inhibit the function of the PD-1/PD-L1 pathway and thereby suppress tumor proliferation. These experiments depended on and grew out of Honjo's collaboration with Freeman and Wood, in which they privately shared with Honjo Freeman's discovery of the PD-L1 and PD-L2 ligands to PD-1; their discovery of the biological function of the PD-1/PD-L1 pathway; their experimental data, including Freeman's data that showed the expression of PD-L1 on various tumors; and Freeman's idea that the PD-1/PD-L1 pathway would be an attractive target for treating cancer.

50. In their meetings and other communications with Honjo, Freeman and Wood did more than merely provide Honjo with well-known principles or explain the state of the art.

51. As part of their collaborative research with Honjo, Freeman and Wood contributed their ideas to the total inventive concept that is claimed in the Patents.

52. Freeman and Wood conceived and made significant contributions to important aspects and features of the inventions claimed in the Patents.

53. Freeman is a joint inventor of each of the Patents.

54. Wood is a joint inventor of each of the Patents.

55. Dana-Farber, as assignee, is a co-owner of each of the Patents.

56. As part of its mission to disseminate innovative patient therapies and scientific discoveries across the United States and throughout the world, Dana-Farber seeks an order correcting inventorship on the Patents. Its objective in pursuing this action is to confirm its ability to grant non-exclusive licenses to companies interested in developing cancer

immunotherapies directed to the PD-1/PD-L1 pathway, in order to ensure broad patient access to the cancer treatments claimed in the Patents.

Count I
(Correction of Inventorship of United States Patent No. 7,595,048)

57. Dana-Farber repeats and realleges the allegations set forth in paragraphs 1 through 56 of the Complaint as if those allegations have been set forth herein.

58. Freeman and Wood each made significant contributions to the conception of the subject matter claimed in the ’048 patent.

59. Freeman and Wood are joint inventors of the ’048 patent.

Count II
(Correction of Inventorship of United States Patent No. 8,168,179)

60. Dana-Farber repeats and realleges the allegations set forth in paragraphs 1 through 59 of the Complaint as if those allegations have been set forth herein.

61. Freeman and Wood each made significant contributions to the conception of the subject matter claimed in the ’179 patent.

62. Freeman and Wood are joint inventors of the ’179 patent.

Count III
(Correction of Inventorship of United States Patent No. 8,728,474)

63. Dana-Farber repeats and realleges the allegations set forth in paragraphs 1 through 62 of the Complaint as if those allegations have been set forth herein.

64. Freeman and Wood each made significant contributions to the conception of the subject matter claimed in the ’474 patent.

65. Freeman and Wood are joint inventors of the ’474 patent.

Count IV
(Correction of Inventorship of United States Patent No. 9,067,999)

66. Dana-Farber repeats and realleges the allegations set forth in paragraphs 1 through 65 of the Complaint as if those allegations have been set forth herein.

67. Freeman and Wood each made significant contributions to the conception of the subject matter claimed in the ’999 patent.

68. Freeman and Wood are joint inventors of the ’999 patent.

Count V
(Correction of Inventorship of United States Patent No. 9,073,994)

69. Dana-Farber repeats and realleges the allegations set forth in paragraphs 1 through 68 of the Complaint as if those allegations have been set forth herein.

70. Freeman and Wood each made significant contributions to the conception of the subject matter claimed in the ’994 patent.

71. Freeman and Wood are joint inventors of the ’994 patent.

WHEREFORE, Dana-Farber Cancer Institute, Inc. respectfully requests that this Court:

a. Determine and declare that Freeman and Wood are joint inventors of the Patents;

b. Order the United States Patent and Trademark Office to correct inventorship of the Patents by adding Freeman and Wood as joint inventors;

c. Determine that this is an exceptional case under 35 U.S.C. § 285 and award Dana-Farber its reasonable attorneys’ fees and costs; and

d. Grant Dana-Farber such other and further relief that this Court deems just and proper.

Respectfully submitted,

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